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International application number: PCT/US04/039728

International filing date: 26 November 2004 (26.11.2004)

Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 60/545,721
Filing date: 18 February 2004 (18.02.2004)

Date of receipt at the International Bureau: 07 January 2005 (07.01.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

1267740

THE UNITED STATES OF AMERICA

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APPLICATION NUMBER: *60/545,721*
FILING DATE: *February 18, 2004*
RELATED PCT APPLICATION NUMBER: *PCT/US04/39728*

Certified by

Jon W Dudas

Acting Under Secretary of Commerce
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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No. ER 754747912 US

INVENTOR(S)

Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
Congxin	Liang	Sunnyvale, California

Additional inventors are being named on the 0 *separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

Hydroxy Compounds as Protein Kinase Inhibitors

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

☐ Customer Number:

OR

☑ Firm or Individual Name	Congxin Liang				
Address	729 West Remington Drive				
Address					
City	Sunnyvale	State	CA	Zip	94087
Country	USA	Telephone	408-718-9689	Fax	408-746-0486

ENCLOSED APPLICATION PARTS *(check all that apply)*

☑ Specification *Number of Pages* 12
☐ CD(s), Number
☐ Drawing(s) *Number of Sheets*
☑ Other (specify) Cover letter
☐ Application Date Sheet. See 37 CFR 1.76

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☑ Applicant claims small entity status. See 37 CFR 1.27.
☐ A check or money order is enclosed to cover the filing fees.
☐ The Director is herby authorized to charge filing fees or credit any overpayment to Deposit Account Number:
☑ Payment by credit card. Form PTO-2038 is attached.

FILING FEE Amount ($): $80.00

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☑ No.
☐ Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,

SIGNATURE Congxin Liang

TYPED or PRINTED NAME Congxin Liang

TELEPHONE 408-718-9689

Date Feb. 18, 2004

REGISTRATION NO. *(if appropriate)*

Docket Number:

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

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FEE TRANSMITTAL for FY 2004

Effective 10/01/2003. Patent fees are subject to annual revision.

☒ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) $80.00

Complete if Known	
Application Number	
Filing Date	Feb. 18, 2004
First Named Inventor	CONGXIN LIANG
Examiner Name	
Art Unit	
Attorney Docket No.	

METHOD OF PAYMENT *(check all that apply)*

☐ Check ☒ Credit card ☐ Money Order ☐ Other ☐ None

☐ Deposit Account:

Deposit Account Number
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The Director is authorized to: *(check all that apply)*

☒ Charge fee(s) indicated below ☐ Credit any overpayments

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FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	80.00

SUBTOTAL (1) ($) 80.00

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

	Extra Claims		Fee from below		Fee Paid
Total Claims		-20** =		X	=
Independent Claims		- 3** =		X	=
Multiple Dependent					=

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($)

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing a brief in support of an appeal	
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37 CFR 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify) _____

*Reduced by Basic Filing Fee Paid SUBTOTAL (3) ($)

(Complete (if applicable))

SUBMITTED BY					
Name (Print/Type)	CONGXIN LIANG	Registration No. (Attorney/Agent)		Telephone	408-718-9689
Signature	Congxin Liang			Date	Feb. 18, 2004

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

This collection of information is required by 37 CFR 1.17 and 1.27. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS.
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Feb. 18, 2004

Congxin Liang
729 W.. Remington Dr.
Sunnyvale, CA 94087
(408)-746-0486
chrisliang03@yahoo.com

Mail Stop: Provisional Patent Application
Commissioner for Patents
Box 1450
Alexandria, VA 22313-1450

Dear Sir or Madam:

Enclosed please find the following documents for a provisional patent application:

- Provisional Application for Patent Cover Sheet
- Fee transmittal for FY 2004
- Credit card payment form (for $80.00)
- Description of the invention: Hydroxy Compounds as Protein Kinase Inhibitors (12 pages)

Please check the list and call me at (408)-718-9689 (mobile) if the application is incomplete.

Best regards,

Congxin Liang

HYDROXY COMPOUNDS AS PROTEIN KINASE INHIBITORS

BACKGROUND OF THE INVENTION

Field of Invention

This invention relates to certain hydroxy compounds and their pharmaceutically acceptable salts as protein kinase inhibitors. The compounds of this invention are therefore useful in treating disorders related to abnormal protein kinase activities such as cancer.

State of the Art

Protein kinases are enzymes that catalyze the phosphorylation of hydroxyl groups of tyrosine, serine, and threonine residues of proteins. Many aspects of cell life (for example, cell growth, differentiation, proliferation, cell cycle and survival) depend on protein kinase activities. Furthermore, abnormal protein kinase activity has been related to a host of disorders such as cancer and inflammation. Therefore, there is a great deal of effort directed to identifying ways to modulate protein kinase activities. In particular, many attempts have been made to identify small molecules which act as protein kinase inhibitors.

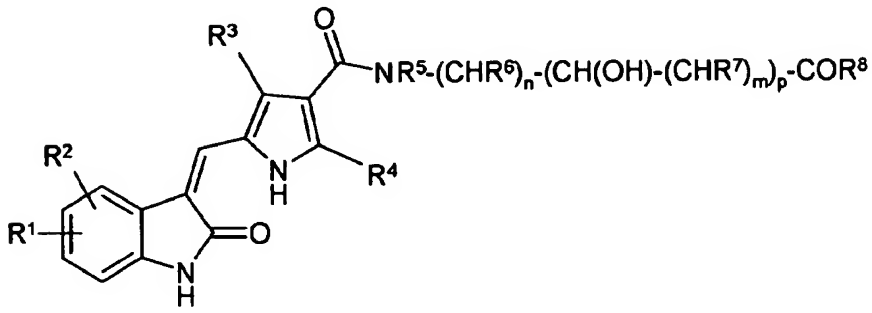
US 60/525,430 and US 60/525,945 disclosed certain hydroxy carboxy compounds as protein kinase inhibitors.

DESCRIPTION OF THE INVENTION

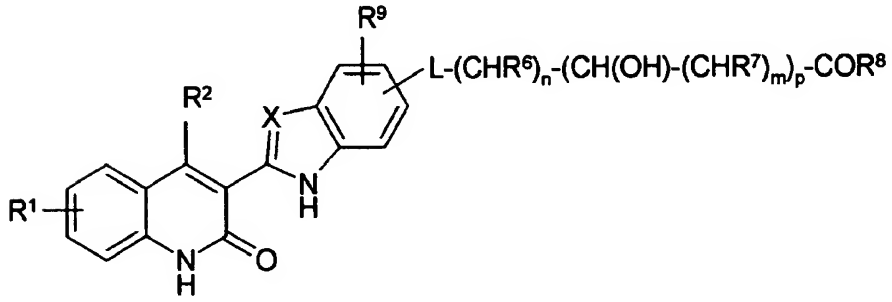
This invention discloses that certain hydroxy carbonyl compounds may have interesting and unexpected properties that advantageously distinguish them from known compounds. They are therefore useful in treating disorders related to abnormal protein kinase activities such as cancer.

One embodiment of this invention is a compound of Formula (I) or (II):

(I)



(II)



wherein:

R^1 is selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, haloalkyl, hydroxy, alkoxy, amino, alkylamino, amide, sulfonamide, cyano, substituted or unsubstituted aryl;

R^2 is selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, haloalkyl, hydroxy, alkoxy, alkoxyalkyl, amino, alkylamino, arylamino;

R^3 is selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, and amide;

R^4, R^5 and R^6 are independently hydrogen or alkyl;

R^7 is hydrogen, alkyl or hydroxyl;

R^8 is selected from the group consisting of alkyl, cyclic alkyl, or $NR^{10}R^{11}$;

R^9 is selected from the group consisting of hydrogen, alkyl, halo, cyano;

X is CR^{12} or N;

L is a di-valent linker selected from the group consisting of -O-, $-NR^{13}$-, $-C(O)-NR^{13}$-, $-NR^{13}-C(O)-NR^{14}$-, $-CHR^{13}-NR^{14}$-, $-CHR^{13}-NR^{14}-C(O)-NR^{15}$-, $-S(O_2)-NR^{13}$-, $-O-CHR^{13}-C(O)-NR^{14}$-, $-CH_2-CH_2-NR^{13}$-;

n, m, and p are independently 0, 1, 2, or 3;

R^{10} and R^{11} are independently hydrogen, or alkyl, or R^{10} and R^{11} together with N is a cyclic ring or heterocyclic ring;

R^{12} is hydrogen, halo, alkyl;

R^{13}, R^{14}, and R^{15} are independently hydrogen or alkyl;

or, a pharmaceutically acceptable salt, its tautomer, a pharmaceutically acceptable salt of its tautomer, prodrug thereof.

Another embodiment of this invention is a compound of Formula (I) or (II) shown above wherein:

R^1 is selected from the group consisting of hydrogen, halo, cyano;

R^2 is selected from the group consisting of hydrogen, hydroxyl, $-NH_2$, $-NHR^{16}$;

R^3, R^4, R^5 and R^6 are independently hydrogen or alkyl;

R^7 is hydrogen, or hydroxyl;

R^8 is selected from the group consisting of $NR^{10}R^{11}$;

R^9 is selected from the group consisting of hydrogen, halo, cyano;

X is CH or N;

n, and p are independently 1, or 2;

m is 0 or 1;

L is a di-valent linker selected from the group consisting of $-C(O)-NR^{13}-$, $-NR^{13}-C(O)-NR^{14}-$, $-CHR^{13}-NR^{14}-C(O)-NR^{15}-$, $-O-CHR^{13}-C(O)-NR^{14}-$, $-S(O_2)-NR^{13}-$;

R^{10} and R^{11} are independently hydrogen, or alkyl, or R^{10} and R^{11} together with N is a cyclic ring or heterocyclic ring;

R^{13}, R^{14}, and R^{15} are independently hydrogen or alkyl;

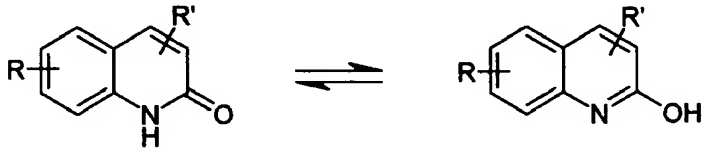
R^{16} is alkyl;

or a pharmaceutically acceptable salt, its tautomer, a pharmaceutically acceptable salt of its tautomer thereof.

It should be understood that all compounds of Formula (I) or (II) have at least one asymmetric center and the stereochemistry at the asymmetric center(s) is(are) either *RS*, *R*, or *S*.

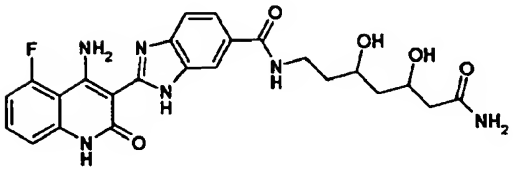
In addition, some of the compounds of Formula (II) may exhibit the phenomenon of tautomerism. As the chemical structures shown in the present invention can only

represent one of the possible tautomeric forms, it should be understood that the invention encompasses any tautomeric form of the drawn structure. For example, any claim to compound **A** below is understood to include tautomeric structure **B**, and vice versa, as well as mixtures thereof.



A **B**

The most preferred compounds of this invention are shown in Tables 1a, 1b, 2a, and 2b.



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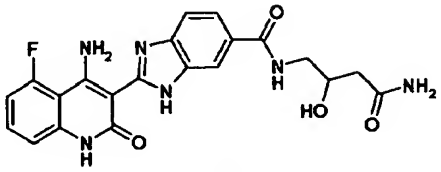

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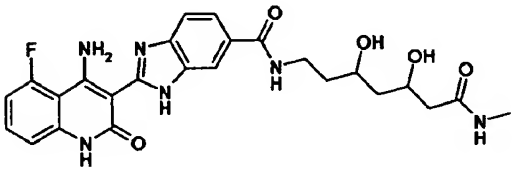

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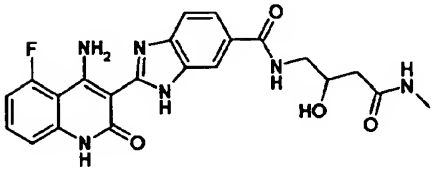

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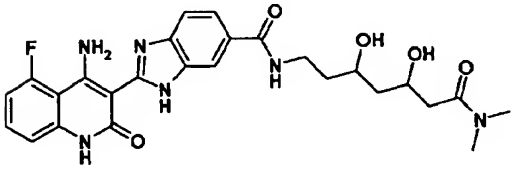

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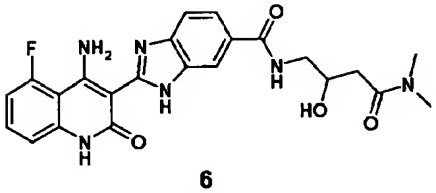

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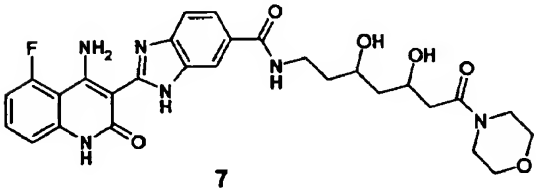

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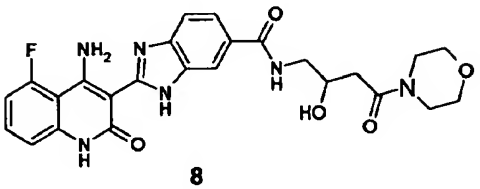

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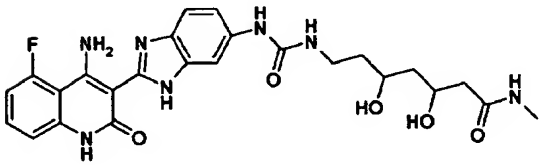

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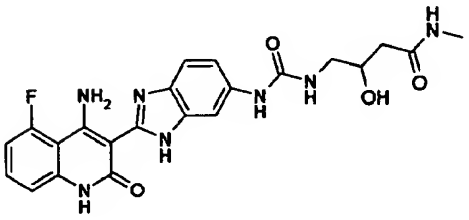

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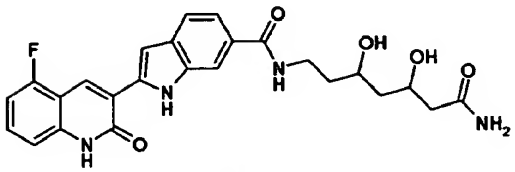
Table 1a



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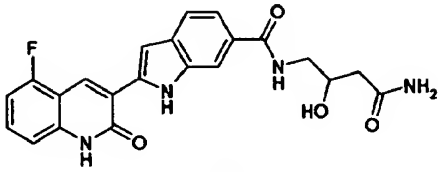

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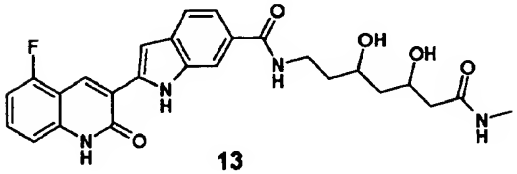

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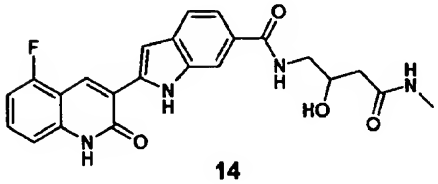

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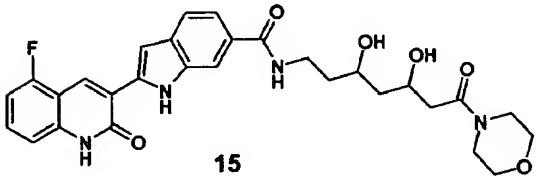

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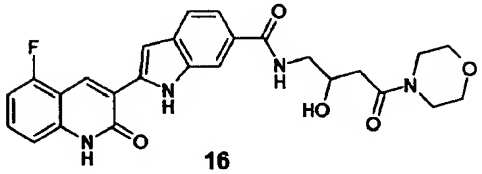

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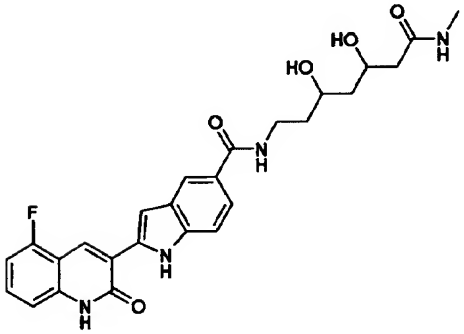

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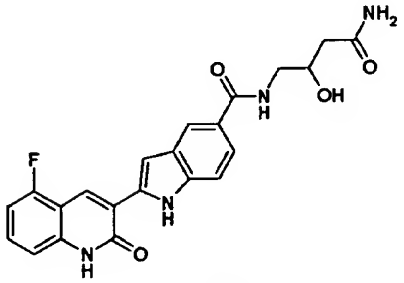

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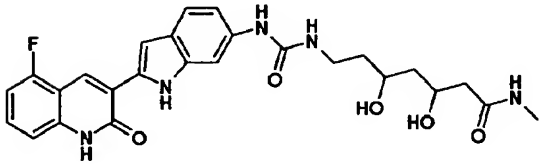

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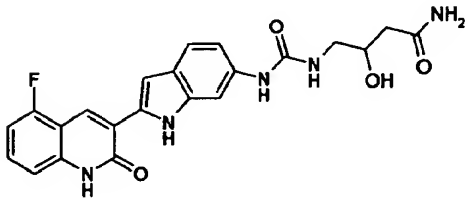

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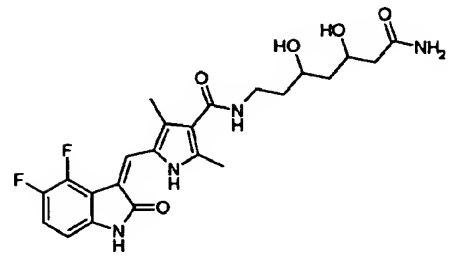
Table 1b



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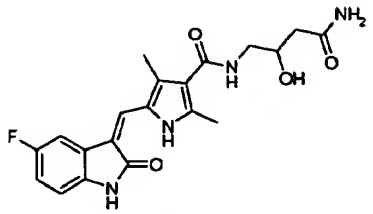

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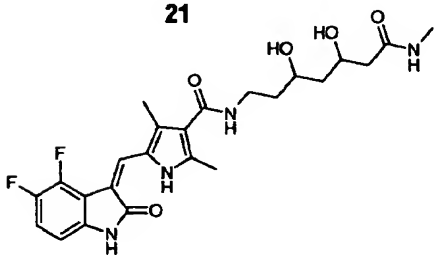

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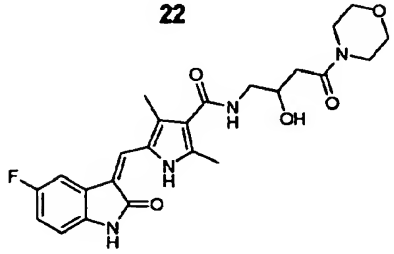

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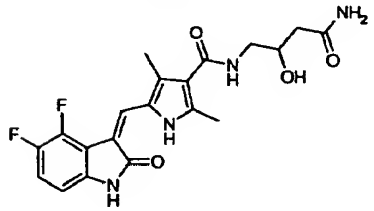

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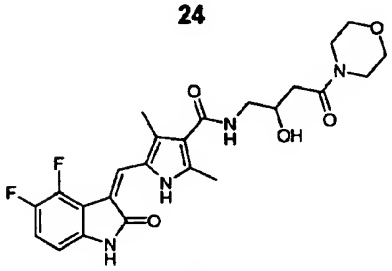

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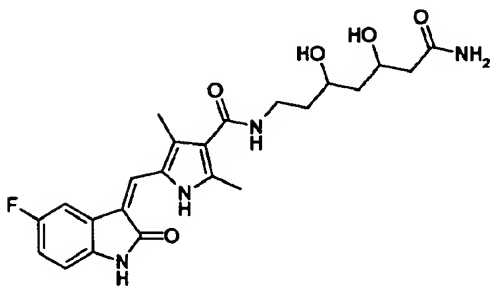
Table 2a



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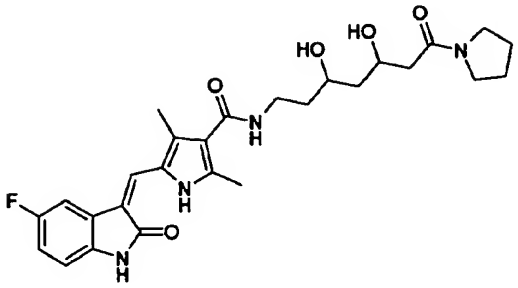

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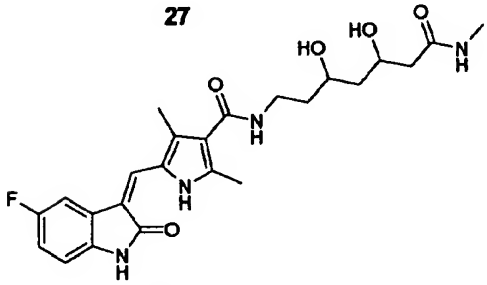

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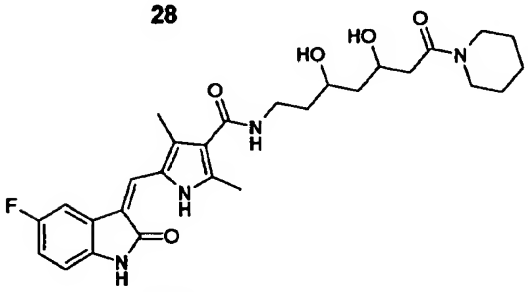

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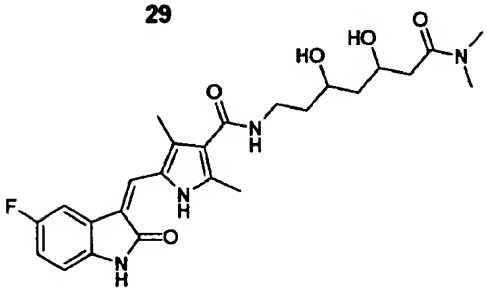

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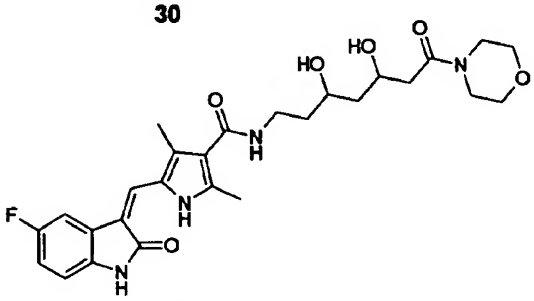

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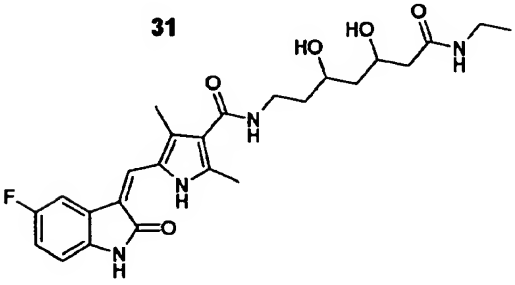

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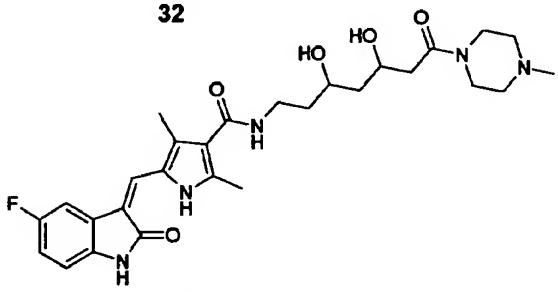

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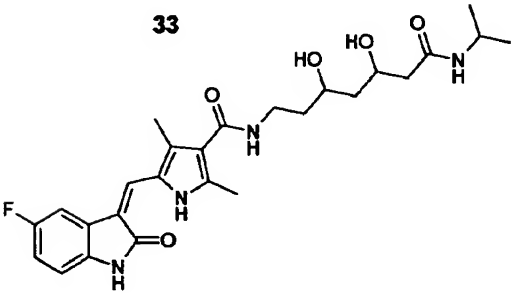

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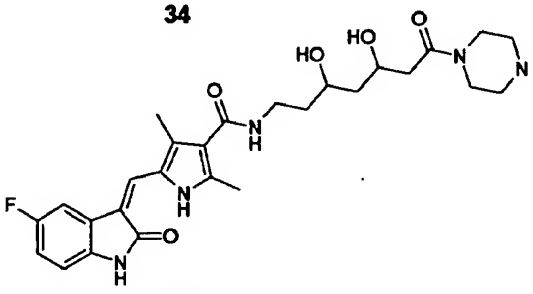

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Table 2b

Utility

The present invention provides compounds capable of regulating and/or modulating protein kinase activities of, but not limited to, VEGFR (Vascular Endothelial Growth Factor Receptor) and/or PDGFR (Platelet-Derived Growth Factor Receptor). Thus, the present invention provides a therapeutic approach to the treatment of disorders related to the abnormal functioning of these kinases. Such disorders include, but not limited to, solid tumors such as glioblastoma, melanoma, and Kaposi's sarcoma, and ovarian, lung, prostate, pancreatic, colon and epidermoid carcinoma. In addition, VEGFR/PDGFR inhibitors may also be used in the treatment of restenosis and diabetic retinopathy.

Furthermore, this invention relates to the inhibition of vasculogenesis and angiogenesis by receptor-mediated pathways, including the pathways comprising VEGF receptors, and/or PDGF receptors. Thus the present invention provides therapeutic approaches to the treatment of cancer and other diseases which involve the uncontrolled formation of blood vessels.

Synthesis of Compounds

The compounds of this invention can be readily synthesized by those skilled in the art starting from the acids disclosed in US 60/525,430 and US 60/525,945.

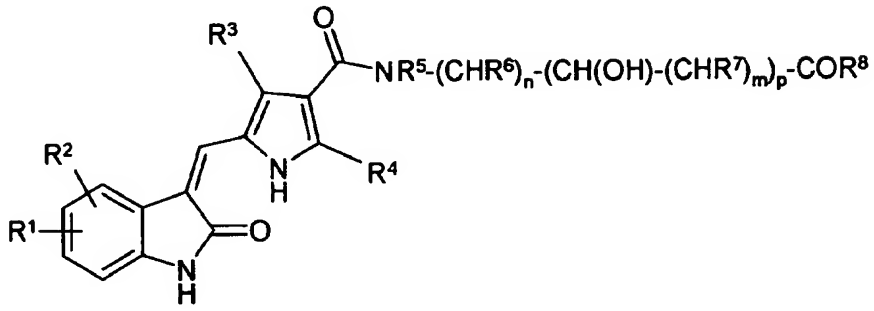
The compounds described herein are presently representative of preferred embodiments, are exemplary, and are not intended as limitations on the scope of the invention. It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention.

The Claims

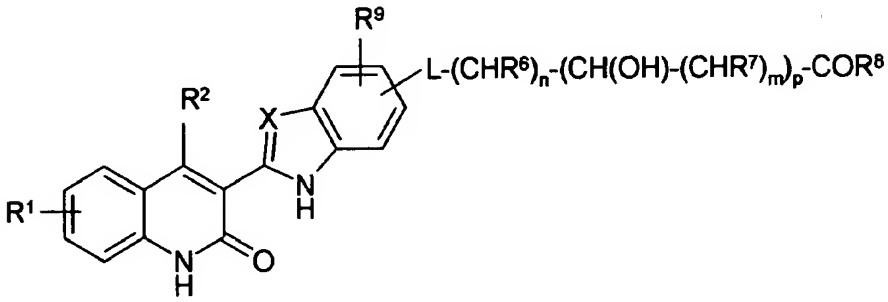
What is claimed is:

1. A compound of Formula (I) or (II):

(I)



(II)



wherein:

R^1 is selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, haloalkyl, hydroxy, alkoxy, amino, alkylamino, amide, sulfonamide, cyano, substituted or unsubstituted aryl;

R^2 is selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, haloalkyl, hydroxy, alkoxy, alkoxyalkyl, amino, alkylamino, arylamino;

R^3 is selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, and amide;

R^4, R^5 and R^6 are independently hydrogen or alkyl;

R^7 is hydrogen, alkyl or hydroxyl;

R^8 is selected from the group consisting of alkyl, cyclic alkyl, or $NR^{10}R^{11}$;

R^9 is selected from the group consisting of hydrogen, alkyl, halo, cyano;

X is CR^{12} or N;

L is a di-valent linker selected from the group consisting of -O-, -NR^{13}-, -C(O)-NR^{13}-, -NR^{13}-C(O)-NR^{14}-, -CHR^{13}-NR^{14}-, -CHR^{13}-NR^{14}-C(O)-NR^{15}-, -$S(O_2)$-NR^{13}-, -O-CHR^{13}-C(O)-NR^{14}-, -CH_2-CH_2-NR^{13}-;

n, m, and p are independently 0, 1, 2, or 3;

R^{10} and R^{11} are independently hydrogen, or alkyl, or R^{10} and R^{11} together with N is a cyclic ring or heterocyclic ring;

R^{12} is hydrogen, halo, alkyl;

R^{13}, R^{14}, and R^{15} are independently hydrogen or alkyl;

or, a pharmaceutically acceptable salt, its tautomer, a pharmaceutically acceptable salt of its tautomer, prodrug thereof.

2. The compound of claim 1, wherein:

R^1 is selected from the group consisting of hydrogen, halo, cyano;

R^2 is selected from the group consisting of hydrogen, hydroxyl, -NH_2, -NHR^{16};

R^3, R^4, R^5 and R^6 are independently hydrogen or alkyl;

R^7 is hydrogen, or hydroxyl;

R^8 is selected from the group consisting of $NR^{10}R^{11}$;

R^9 is selected from the group consisting of hydrogen, halo, cyano;

X is CH or N;

n, and p are independently 1, or 2;

m is 0 or 1;

L is a di-valent linker selected from the group consisting of -C(O)-NR^{13}-, -NR^{13}-C(O)-NR^{14}-, -CHR^{13}-NR^{14}-C(O)-NR^{15}-, -O-CHR^{13}-C(O)-NR^{14}-, -$S(O_2)$-NR^{13}-;

R^{10} and R^{11} are independently hydrogen, or alkyl, or R^{10} and R^{11} together with N is a cyclic ring or heterocyclic ring;

R^{13}, R^{14}, and R^{15} are independently hydrogen or alkyl;

R^{16} is alkyl;

or a pharmaceutically acceptable salt, its tautomer, a pharmaceutically acceptable salt of its tautomer thereof.

3. The compound or salt of claim 1, wherein the compound is selected from the compounds **1-10** in Table 1a.

4. The compound or salt of claim 1, wherein the compound is selected from the compounds **11-20** in Table 1b.

5. The compound or salt of claim 1, wherein the compound is selected from the compounds **21-36** in Table 2a and Table 2b.

6. A method for the modulation of the catalytic activity of a protein kinase with a compound or salt of any one of claims 1, 2, 3, 4, or 5.

7. The method of claim 6, wherein said protein kinase is selected from the group consisting of VEGF receptors, PDGF receptors.